

**REMARKS/ARGUMENTS**

In response to the advisory action issued by the Office November 16, 2009, Applicants have presented the included amendments and arguments and a request for continued examination.

Reconsideration of this Application and entry of this Amendment is respectfully requested. By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. Cf. *Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

No new matter has been added as a result of the present amendments.

**In the Claims**

Claims 1-12, 14-16 and 24-26 are pending in this application. Claim 10 has been previously withdrawn from consideration. Claims 13 and 17-23 have been previously cancelled. In view of the Examiner's earlier restriction requirement, Applicants retain the right to present claim 10 in a divisional application.

Solely in an effort to expedite prosecution of the present case and not to acquiesce to the Office's rejections, claims 1, 16 and 24 have been amended to define R1 and R2 as hydrogen. Support can be found, for example in claim 4, which has been amended to remove such limitations. Claim 1 has further been amended to recite "wherein at least one of R3, R4, R5, R6, R7, R8, R9, R10 and R11 is a linker and the linker joins the therapeutic component and the efficacy enhancing component."

Claims 9 and 11 have been cancelled.

**35 U.S.C. §102 Rejections**

Claims 1, 7, 9 and 16 are rejected under 35 U.S.C. §102(b) as being anticipated by Collins et al. (WO 01/92288, herein after "Collins"). The Office asserts that Collins discloses compositions which are embraced by the instant claimed invention. Applicants respectfully disagree.

As the Office is aware, a claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in a claim is found, either expressly or inherently described, in a single prior art reference. MPEP §2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 USPQ2d 1051 (Fed. Cir. 1987). A claimed invention is anticipated only when it is “known to the art in the detail of the claim.” *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). In other words, not only must the limitations of the claim be shown in a single prior art reference, the limitations must be “arranged as in the claim.” *Id.*

Applicants assert that Collins does not teach a pharmaceutical conjugate comprising a therapeutic component covalently coupled to an efficacy enhancing component as presently claimed. The presently amended claims teach an adamantine amine efficacy enhancing component linked to a therapeutic component at a position other than at the amine.

In contrast, Collins teaches that antibiotics that contain an amine or amide group “can be linked to the TC- of IF-binding agent through that functional moiety, using standard reactions for covalent bond formation to a nitrogen atom” (Page 85, lines 3-5). As such, the adamantine HCl listed on Page 92, as pointed out by the Office, is covalently bonded to the TC- of IF-binding agent through the amine group, not at another location as is presently claimed.

In light of the above, Collins does not teach the compositions presently claimed, and therefore, fails to teach each and every element of the presently amended claims. As such, Applicants request reconsideration of claims 1, 7, 9 and 16 as amended.

### **35 U.S.C. §103 Rejections**

Claims 1-6, 7, 8, 9, 11-12, 14-16 and 24-26 are rejected under 35 U.S.C. §103(a) as being obvious over Desantis, Jr. (US 2001-0047012, hereinafter “Desantis”) in view of Collins. The Office suggests that Desantis teaches combination therapy and Collins teaches pharmaceutical conjugates comprising a bioactive agent that is covalently bound to a linker. Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

As discussed above, Collins does not teach a pharmaceutical conjugate comprising a therapeutic component covalently coupled to an efficacy enhancing component as presently claimed. The presently amended claims teach an adamantine amine efficacy enhancing component linked to a therapeutic component at a position other than the amine.

In contrast, Collins teaches that antibiotics containing an amine or amide group "can be linked to the TC- or IF-binding agent through that functional moiety, using standard reactions for covalent bond formation to a nitrogen atom" (Page 85, lines 3-5). As such, the adamantine HCl listed on Page 92, as pointed out by the Office, is

covalently bonded to the TC- or IF-binding agent through the amine group, not at another location as presently claimed.

The Office attempts to combine the teachings of Collins with those of Desantis which teaches methods of treating glaucoma using a combination therapy. Desantis' combination therapy requires the "use of a glutamate antagonist and an IOP controlling agent, dosed separately or in combination for the treatment of persons suffering from glaucoma or ocular hypertension." (paragraph [0006]). Desantis does not teach a glutamate antagonist covalently linked to an IOP controlling agent, nor is it even suggested that the two are linked. One skilled in the art would clearly understand that the glutamate antagonist and the IOP controlling agent are not linked. As such, this teaching does not remedy the deficiencies of Collins.

Further, the combination of references alone or in combination do not teach an adamantine amine efficacy enhancing component linked to a therapeutic component at a position other than the amine as presently claimed. The presently claimed conjugated component, therefore, includes a primary amine, which the combination of references does not. Desantis teaches delivery of amantadine or memantine, but as discussed above, it is not linked, or conjugated, with a therapeutic component as presently claimed, in fact, they are not linked at all, and therefore, is irrelevant with regard to the present claims. On the other hand, Collins links a TC- or IF-binding agent to an antibiotic resulting in a secondary or even a tertiary amine. Again, this is not the same as presently claimed. A skilled artisan armed with Desantis and Collins is not going to be motivated to link a therapeutic agent to an amantadine, as taught by Collins, at a location other than the amine group; there is simply no motivation in the art to do so.

In light of the above, Applicants assert that a proper *prima facie* case of obviousness has not been established with regard to claims 1-6, 7, 8, 9, 11-12, 14-16 and 24-26 as amended. Therefore, Applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

**Conclusion**

Applicants respectfully request that a timely Notice of Allowance be issued in this case. The fees were paid on the previously filed response filed this day, January 11, 2010 and no further fees are believed due at this time. The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment and any other fees due in this case to Deposit Account No. 01-0885.

Respectfully submitted,

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